Optimal designs for compartmental models with unknown/non-constant transfer coefficients

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SUMMARY

Numerical procedures for obtaining optimal designs for compartmental models when there is not an analytical solution are proposed. The ideas can be extended to other (non-compartmental) ordinary-differential-equation systems without analytical solutions.

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Optimal designs for compartmental models and ordinary-differential-equation systems

- Known set of techniques for obtaining optimal designs when the model is linear in the parameters.
- For non-linear models (but given by an analytical expression) the usual approach is to linearize it. In this case initial values are needed for the non-linear parameters (*locally optimal* designs)
- Problems when it is not possible to obtain an analytical expression for the model. Example: model described by a system of ordinary differential equations (ODE) without a general solution. In this situation, the techniques used routinely by the optimal design theory cannot be employed.

Method 1

- Virtual model
- Numerical derivatives

Method 2

Extended systems

Method 3

Compartmental-like models

- Models given by Equation (1)

$$\begin{cases} \dot{x}(t) = Ax + b(t), t \geq 0 \\ x(0) = x_0 \end{cases} \qquad (1)$$

(for instance compartmental models), where $x_i(t)$ denotes the amount or content of species in compartment i at a time t.
A is the $m \times m$ *system matrix* given by $a_{ij}=$ g(k_{ij}), where k_{ij} are the transfer constants
$b_i(t)$ is the input rate into compartment i from the environment

- The solution of Equation (1) when the coefficients a_{ij} are constants is

$$x(t) = x_0 \exp(At) + \exp(At) * b(t) \qquad (2)$$

(see Bates and Watts, 1988), where "$*$" denotes convolution,

$$\exp(At) * b(t) = \int_0^t \exp[(t-\tau)A] b(\tau) d\tau$$

- Then, if $b(t)$ and x_0 are not dependent on θ_j,

$$\dot{x}_{(j)}(t) = A x_{(j)}(t) + A_{(j)} x(t)$$

Now, mimicking Equation (2) $x_{(j)}(t) = \exp(At) * \left[A_{(j)} x(t)\right]$, and substituting $x(t)$ from (2)

$$x_{(j)}(t) = \exp(At) * A_{(j)} \exp(At) x_0 + \exp(At) * A_{(j)} \exp(At) * b(t) \quad ,$$

that is the derivative function

- In particular, if the input occurs for $t=0$, $x(0)=x_0$ and $b(t)=0$ for $t>0$, and then $x_{(j)}(t) = \exp(At) * A_{(j)} \exp(At) x_0$

Example: Biokinetic model of Ciprofloxacin and Ofloxacin

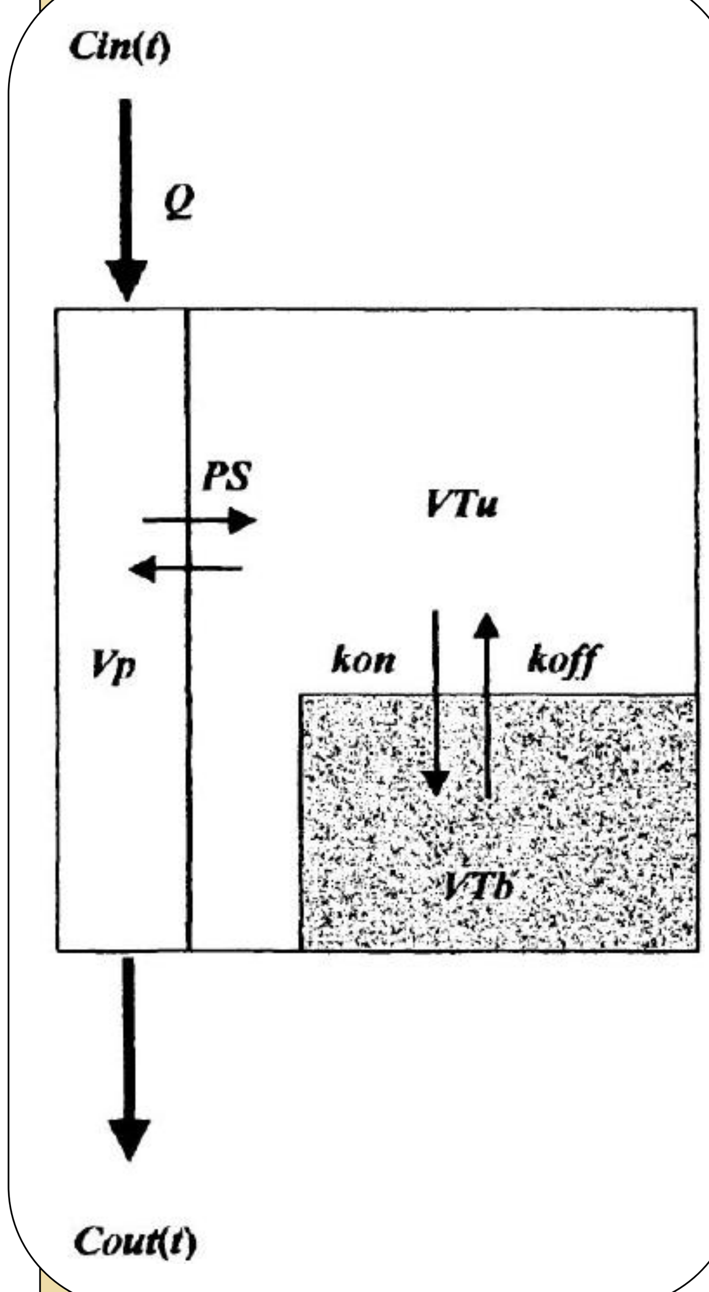
It is a physiological (non-compartmental) model that produces the following differential-equation system (Sánchez Navarro et al, 1999):

$$c'_{out}[t] + \left(\frac{Q}{V_p} + \frac{PS}{V_p}\right) c_{out}[t] - \frac{PS}{V_p} c_{Tu}[t] = \frac{Q}{V_p} c_{in}[t]$$
$$c'_{Tu}[t] + \left(\frac{PS}{V_{Tu}} + k_{on}\right) c_{Tu}[t] - \frac{PS}{V_{Tu}} c_{out}[t] - k_{off} \frac{V_{Tb}}{V_{Tu}} C_{Tb}[t] = 0$$
$$c'_{Tb}[t] + k_{off} c_{Tb}[t] - k_{on} \frac{V_{Tu}}{V_{Tb}} c_{Tu}[t] = 0 \text{ with initial conditions}$$
$$c_{out}[0] = 0, c_{Tu}[0] = 0, c_{Tb}[0] = 0$$

The differential-equation system for the model can be expressed after some substitutions as

$$x'_1(t) = -5.87256 x_1(t) + 2.7893 x_2(t) + 3.08325 c_{int}(t)$$
$$x'_2(t) = 0.423335 x_1(t) + (-k_{on} - 0.423335) x_2(t) + 0.15598 k_{off} x_3(t)$$
$$x'_3(t) = 6.411 k_{on} x_2(t) - k_{off} x_3(t)$$

with $x_1(0) = x_2(0) = x_3(0) = 0$ and t in days. According to Sánchez (2007), c_{in}(t) $= 13610.1 t e^{-11.216t}$ will be used.



Optimal designs

Optimal times when using exponential covariance

	Number of observations 2	3	4
D-opt	1.574	1.570	2.111
	6.016	5.154	15.166
		8.312	29.460
			43.942
A-opt	1.463	2.154	2.111
	6.689	19.854	15.166
		50.808	29.460
			43.942

Efficiency study:

D-opt: 2-point design is the best (then 3-point)

A-opt: 3-point design is the best (then 4-point)

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mODa Model-Oriented Data Analysis and Optimum Design

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